REMARKS

Amendments to the Specification

The title has been amended as suggested by the Examiner. No new matter has been added.

The "Related Applications" section of the specification has been amended to reflect the status of the priority applications. No new matter has been added.

The specification has been further amended to correct typographical errors, to remove embedded hyperlinks, to provide the current address of the American Type Culture Collection, and to insert SEQ ID NOs, as requested by the Examiner. Accordingly, a revised sequence listing is also being submitted herewith. No new matter has been added.

Amendments to the Claims

Claims 1-15 were pending in the application. Claims 9-12 have been cancelled, without prejudice, as being drawn to a non-elected invention. Claims 1, 3-5, 7-8 and 13-14 have been amended to correct the typographical errors and address the issues raised by the Examiner. New claims 16-27 have been added. Accordingly, Claims 1-8 and 13-27 are currently pending.

Support for the foregoing amendments is found throughout the specification and claims as originally filed. Specifically, support for the amendments to claims 1, 3-5, 7-8 and 13-14 and new claims 16-27 can be found at least in the following portions of the specification as originally filed:

New Claims	Support
1	Page 4, lines 1-10; page 38, lines 25-31
3	Page 4, lines 1-10
4	Claim 4 as originally filed
5	Page 38, lines 15-20; page 4, lines 1-10; page 38, lines 25-31
7	Page 4, lines 1-10
8	Claim 8 as originally filed
13	Page 4, lines 1-10; page 38, lines 25-31
14	Claim 14 as originally filed
16	Claim 1 as originally filed
17	Claim 5 as originally filed
18	Claim 6 as originally filed
19	Claim 7 as originally filed

20	Claim 13 as originally filed
21-25	Page 57, lines 17-21
26-27	Page 42, lines 6-15

No new matter has been added by way of these amendments. Amendment to the claims should in no way be viewed as acquiescence to any rejection. Applicants reserve the right to pursue the claims as originally filed in this or subsequent applications.

Applicants' Claim to Domestic Priority Under 35 U.S.C. §120

The Examiner acknowledges Applicants' priority claim for domestic priority with regard to USSN 09/628129 (U.S. Patent No. 6,613,327) and states that the '327 patent "provides adequate support under 35 U.S.C. §112 for subject matter claimed in the instant application." However, the Examiner asserts that the application, USSN 09/362812, upon which priority is also claimed "fails to provide adequate support under 35 U.S.C. §112 for subject matter claimed in the instant application . . ."

Applicants respectfully traverse this rejection. It is not necessary that exact literal support for the presently claimed invention be present in each priority application to entitle the present application to the benefit of such priority applications. It is well established that the requirement for claiming priority under 35 U.S.C. §120 is that the specification of the priority application satisfy the requirements set forth in 35 U.S.C. §112, first paragraph (See, *e.g., New Railhead Mfg. L.L.C. v. Vermeer Mfg. Co.*, 298 F.3d 1290 at 1296, 63 U.S.P.Q2d 1843 (Fed. Cir. 2002); *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d 956 at 979, 63 U.S.P.Q.2d 1609 (Fed. Cir. 2002)). With respect to the presently claimed methods, this requirement is met for both priority applications. Accordingly, the present claims are entitled to the benefit of the complete priority claim listed on page 1 of the specification, which includes priority to USSN 09/628129 (U.S. Patent No. 6,613,327) and USSN 09/362812 (now abandoned).

In particular, the specification of the priority application, USSN 09/362812, teaches, for example, that inhibition of the costimulation of T cells can inhibit spontaneous abortion in a subject. Accordingly, the presence or detection of molecules associated with such costimulatory signals would be a diagnostic or prognostic tool for identifying subjects who are at risk for, or

who are undergoing, a spontaneous abortion, as currently claimed, *e.g.*, by detecting the presence or level of mRNA of one or more of particular molecules, such as IL-2.

Overall, Applicants' teachings contained within the four corners of the priority application, USSN 09/362812, combined with the level of skill in the art, which includes knowledge of the mechanisms by which T cells respond to foreign proteins, fully support and enable the presently claimed methods. Accordingly, based at least on the foregoing, the present application is entitled to the benefit of each of the priority applications.

Information Disclosure Statement Submitted July 15, 2004

Pursuant to the Examiner's request, the dates for References B10-B12, C4 and C5 of the Information Disclosure Statement filed on July 15, 2004 are as follows:

B10: GenBank Accession Number U90273 for homo sapiens CTLA-4 mRNA, partial cds, Jan. 5, 1999

B11: GenBank Accession Number U90271 for Rattus Norvegicus CTLA-4 mRNA, complete cds, Jan. 5, 1999

B12: GenBank Accession Number U90270 for mus musculus CTLA-4 mRNA, partial cds, Jan. 5, 1999

C4: Larrick, J.W. (1997) "CTLA4-IG-antiCD40 fusion protein for immunotherapy ," (abstract) Federal Research in Progress, National Technical Information Services (NTIS), Springfield, VA; Retrieved from Dialog Information Services, Palo Alto, CA Access No. 285978

C5: Larsen, C.P. (1997) "Activation, apathy, anergy, apoptosis in transplantation," (abstract) Federal research in Progress, National Technical Information Services (NTIS), Springfield, VA; Retrieved from Dialog Information Services, Palo Alto, CA Access No. 285737

Objection to Claims 1 and 5 as Lacking Antecedent Basis

Claims 1 and 5 are objected to as lacking antecedent basis for recitation of "spontaneous abortion." Specifically, the Examiner states that the "specification appears to provide antecedent basis only for a more narrow recitation of 'immune-mediated spontaneous abortion' . . . " Applicants respectfully disagree.

In particular, Applicants respectfully direct the Examiner's attention to the present specification, for example, at page 7, lines 15-16, which states that "the term 'immune mediated abortion' includes spontaneous termination of a pregnancy, *e.g.*, a miscarriage." Based at least on the foregoing, the present specification provides antecedent basis for claims 1 and 5.

Rejection of Claims 1-3, 5-7 and 13-15 USC 112, Second Paragraph

Claims 1-3, 5-7 and 13-15 are rejected under 35 USC 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) Claims 1 and 5

The Examiner contends that claims 1 and 5 are "incomplete for omitting essential steps or ingredients, such omission amounting to a gap between the steps." In particular, the Examiner states that "there appears to be insufficient correlative step (e.g. what level of a given molecule is indicative of an increased risk of spontaneous abortion?)."

Applicants respectfully disagree. However, to expedite prosecution, claims 1 and 5 have been amended to recite the further step of "determining if the presence or level of said mRNA is normal, wherein an abnormal presence or level of said mRNA indicates that the subject is at risk for developing spontaneous abortion." Support for this amendment can be found, for example, at least at page 41, line 31 through page 42, line 5, and at page 42, line 24 -29. Applicants submit that the amendments to claims 1 and 5 render the rejection moot.

(B) Claims 3 and 7

The Examiner contends that claims 3 and 7 are indefinite due to the improper recitation of the species "IL-10" among the Markush group for "inflammatory cytokines." In particular, the Examiner asserts that IL-10 is known in the art as an "anti-inflammatory cytokine," and, thus, the metes and bounds of the phrase "inflammatory cytokines" are vague and indefinite.

Applicants respectfully disagree. However, in the interest of expediting prosecution, claims 3 and 7 have been amended to delete IL-10 from the Markush group. Therefore, this rejection is now moot.

(C) Claim 13

Claim 13 is rejected s being indefinite in the recitation of the relative term "appropriate control." The Examiner is of the opinion that the specification does not provide a sufficient standard for ascertaining which control would be appropriate and, as a consequence, one of ordinary skill in the art would not be apprised of the metes and bounds of the invention.

Applicants respectfully traverse this rejection. The fact that claim language, including terms of degree, may not be precise does not automatically render the claim indefinite under 35 USC 112, second paragraph. *Seattle Box co., v. Industrial Crating & Packing, Inc.*, 731 F.2d 818, 221 USPQ 568 (Fed. Cir. 1984). Acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification. MPEP 2173.05(b). The breadth of a claim is not to be equated with indefiniteness. *In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA 1971).

One of ordinary skill in the art would understand what is claimed in claim 13 based at least on the teachings of the present specification, combined with the level of skill in the art at the time of the present invention. In particular, the specification provides ample guidance as to what would be an "appropriate control," for example, at page 41, line 31 through page 42, line 5:

> In order to determine if the level of one or more of an adhesion molecule, an inflammatory cytokine, and/or an immune cell surface antigen in a biological sample from a test subject is abnormal, the level of one or more of an adhesion molecule, an inflammatory cytokine, and/or an immune cell surface antigen from the test subject is ***compared, for example, to the average level of those molecules determined from women who have had normal pregnancies.*** If the level of those molecules determined in the test subject is higher (*i.e.*, statistically significantly higher) than the levels for normal pregnancies, the test subject is diagnosed as being at risk for developing immune-mediated spontaneous abortion. [emphasis added].

In view of the foregoing, Applicants submit that one of ordinary skill in the art would clearly understand the metes and bounds of the invention from the disclosure. However, to expedite prosecution, and in no way acquiescing to the Examiner's rejection, claim 13 has been amended to recite "...comprising comparing the level of mRNA of one or more of an adhesion molecule, an inflammatory cytokine, or an immune cell surface molecule in the biological

sample obtained from said subject, or isolate of said sample, to the level of mRNA of one or more of an adhesion molecule, an inflammatory cytokine, or an immune cell surface molecule in ***a biological sample, or isolate of said sample, from one or more subjects who have had normal pregnancies."*** Applicants submit that the amendment to claim 13 renders the rejection moot.

(D) Claim 5

The Examiner contends that claim 5 is indefinite in the recitation of a "diagnostic method for determining whether a subject is suffering from spontaneous abortion." In particular, the Examiner is of the opinion that "it is unclear whether the method is directed to the moment in time when the loss of the products of conception actually occurs, to detection of the outcome of the loss, or to diagnosing the cause of infertility."

Applicants respectfully disagree. However, to expedite prosecution, claim 5 has been amended to recite "[a] diagnostic method for determining whether a subject is ***undergoing*** a spontaneous abortion." Support for this amendment can be found at, for example, page 38, lines 17-20. Applicants submit that the amendment to claim 5 renders the rejection moot.

(E and F) Claims 13 and 14

Claim 13 has been amended to correct its dependency. Further, claim 14 has been amended to provide proper Markush format. Therefore, the rejections pertaining to claims 13 and 14 are now moot.

Rejection of Claims 1-3, 5-7 and 13-15 USC 112, First Paragraph

Claims 1-3, 5-7 and 13-15 are rejected under 35 USC 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Each of the issues raised by the Examiner is addressed below.

A. The Examiner contends that a person of skill in the art is not enabled to "determine whether the difference in the mRNA levels between the abortion-prone and control

samples is statistically significant or reproducible." The Examiner further states that "[t]here is insufficient enabling disclosure of the numbers of mice sampled, the numbers of times the experiments were repeated, the deviation of values between different experiments, etc., beyond the statement that "duplicate samples" were processed (page 51 bottom paragraph)." Applicants respectfully traverse this rejection.

Compliance with the enablement requirement of 35 U.S.C. §112, first paragraph, does not turn on whether an example is disclosed. An example may be "working" or prophetic. An applicant need not have actually reduced the invention to practice prior to filing. MPEP 2164.02. The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908 (CCPA 1970) (lack of working examples or lack of evidence that the claimed invention works as described should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement). A single working example in the specification for a claimed invention is enough to preclude a rejection which states that nothing is enabled since at least that embodiment would be enabled. MPEP 2164.02.

Applicants submit that even though the MPEP makes clear that ***working examples are not required for an invention to be enabled***, the instant specification nevertheless provides working examples which demonstrate a correlation between elevated expression of particular genes and increased risk of spontaneous abortion. The Examiner's comments regarding lack of disclosure of the number of mice sampled, the number of times the experiments were repeated and whether the data is statistically significant are criticisms of the ***quality of the experiments*** provided in the working examples. The standard for enablement simply does not require that working examples provide statistically significant data. Rather, the test is whether one of ordinary skill in the art could practice the claimed invention without undue experimentation.

Based at least on the foregoing, the rejection of claims 1-3, 5-7 and 13-15 under 35 U.S.C. §112, first paragraph, for lack of enablement is improper and respectfully request the Examiner to withdraw the rejection.

B. The Examiner contends that the elected claims are not enabled with respect to the degree of elevation of mRNA which would be prognostic or diagnostic for each of the claimed molecules.

Applicants respectfully traverse this rejection. Applicants submit that the instant specification provides sufficient guidance such that one of ordinary skill in the art could practice the methods claimed in claims 1-3, 5-7 and 13-15 without undue experimentation.

In order for a claimed invention to be enabled, the standard is not whether or not experimentation is necessary to practice the claimed invention. Rather, the standard is whether or not the experimentation necessary to practice the claimed invention is undue (See *In re Wands*, 858 F.2d 731 at 737 (Fed.Cir. 1988)). Thus, enablement is not precluded by the necessity for some experimentation, and a considerable amount of experimentation is permitted. *In re Wands*, *supra*. A patent need not teach, and preferably omits, what is well known in the art. *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 3 USPQ2d1737 (Fed. Cir. 1987).

Applicants submit that the claims are sufficiently enabled by the specification with respect to the degree of mRNA elevation that is prognostic or diagnostic of spontaneous abortion. In the instant application, general guidance is provided in the specification as to ranges of elevated gene expression that are diagnostic or prognostic of a subject being at risk for spontaneous abortion (see, *e.g.*, page 42, first paragraph). Moreover, the application provides working examples (see, *e.g.*, Example 11 and Figure 6) that teach the measurement of relative mRNA levels (presented as an average from pooled mRNAs from multiple mice) for various genes in placental tissue of normal mice and mice at increased risk for, or which show high incidence of, spontaneous abortion. In particular, the examples teach that VCAM-1 expression is elevated at the mRNA level in resorbing placental tissue as compared to normal placental tissue by approximately 2-fold (Figure 6A), P-selectin by approximately 1.5 fold (Figure 6D), IL-2 by approximately 9-fold (Figure 6F), IL-10 by approximately 9-fold (Figure 6G), IL-12 by approximately 7-fold (Figure 6H), IL-11 by approximately 4.5-fold (Figure 6I), TNFα by approximately 6-fold (Figure 6J), IL-1B by approximately 2.5-fold (Figure 6K), TGF by approximately 3.5-fold (Figure 6L), B7.1 by approximately 9.5-fold (Figure 6M), B7.2 by approximately 8-fold (Figure 6N), CD4 by approximately 6-fold (Figure 6O), CD8 by approximately 17-fold (Figure 6P), RANTES by approximately 22-fold (Figure 6Q), IL-6 by

approximately 8.5-fold (Figure 6R), mGL50 by approximately 2-fold (Figure 6S), mICOS by approximately 1.5-fold (Figure 6T), and IFNγ by approximately 5-fold (Figure 6V) (page 54, paragraph 1 and 2). INOS expression is shown to be diminished at the mRNA level in resorbing placental tissue as compared to normal placental tissue by approximately 30% (Figure 6U), and E-selectin by over 30-fold (Figure 6E) (page 54, paragraph 1 and 2).

Based at least on the foregoing, the specification provides sufficient direction and guidance such that an ordinarily skilled artisan could determine the degree by which mRNA levels must be modulated to achieve prognostic or diagnostic utility for spontaneous abortion. In addition, Applicants submit that the state of the art was high at the time of the present invention. Accordingly, experiments designed to measure mRNA for particular genes, *e.g.*, in disease and control groups, and to extract from that data which degree of gene overexpression correlates with a particular disorder or predisposition to a disorder, *e.g.*, increased risk of spontaneous abortion, would be nothing more than routine. Therefore, one of ordinary skill in the art could use the claimed invention without undue experimentation based upon the teachings of the instant specification and armed with the knowledge of one of ordinary skill in the art.

In view of the foregoing, Applicants respectfully request that rejection of claims 1-3, 5-7 and 13-15 under 35 USC §112, first paragraph for lack of enablement be reconsidered and withdrawn.

C. The Examiner contends that the elected claims are not enabled with respect to the genus of "adhesion molecules." The Examiner further contends that the elected claims are not enabled for the genus of "inflammatory cytokines."

Applicants respectfully traverse this rejection. It is not necessary to enable ***all*** species of the claimed invention, but rather a ***representative number*** of species. Applicants submit that a representative number of species of "adhesion molecules" and "inflammatory cytokines" has been taught by the immediate disclosure to enable the claimed invention.

In particular, with respect to adhesion molecules, Applicants have provided detailed experiments which indicate that VCAM-1 protein expression is elevated in the resorbing placentas of abortion prone mice as compared to placental tissue of normal mice by monitoring binding of 125I-labeled VCAM-1 antibody (see, *e.g.*, Example 10 at page 53-54). Further

experiments provided in the specification demonstrate that VCAM-1 and P-selectin mRNA levels are elevated by approximately 2-fold and 1.5-fold, respectively, in resorbing placental tissue as compared to normal placental tissue, while E-selectin mRNA level is decreased by over 30-fold in resorbing placental tissue as compared to mRNA from normal placental tissue (see, *e.g.*, Example 11 at page 54, first and second paragraph). Thus, each of the adhesion molecules VCAM-1, P-selectin and E-selectin has been identified as having altered expression in placental tissue from abortion prone mice as compared to that from normal mice. Accordingly, a representative number of species of adhesion molecules has been taught to enable the claimed invention.

Similarly, with respect to inflammatory cytokines, Applicants provide detailed experiments which indicate that expression of each of the claimed inflammatory cytokines, IL-2, IL-10, IL-12, IL-11, TNFα, IL-1B,TGF, RANTES, IL-6 and IFNγ, is elevated at the mRNA level in resorbing placental tissue of abortion prone mice as compared to placental tissue of normal mice. Specifically, as described above, IL-2 mRNA is shown to be elevated by approximately 9-fold (Figure 6F), IL-10 by approximately 9-fold (Figure 6G), IL-12 by approximately 7-fold (Figure 6H), IL-11 by approximately 4.5-fold (Figure 6I), TNFα by approximately 6-fold (Figure 6J), IL-1B by approximately 2.5-fold (Figure 6K), TGF by approximately 3.5-fold (Figure 6L), RANTES by approximately 22-fold (Figure 6Q), IL-6 by approximately 8.5-fold (Figure 6R) and IFNγ by approximately 5-fold (Figure 6V). Thus, a representative number of species of inflammatory cytokines has been taught by the immediate disclosure to enable the claimed invention.

In view of the foregoing, Applicants respectfully request that rejection of claims 1-3, 5-7 and 13-15 under 35 USC §112, first paragraph for lack of enablement be reconsidered and withdrawn.

D. The Examiner contends that the "specification does not provide sufficient objective evidence that supports the predictive or diagnostic nature of the claimed methods when applied to 'biological samples' of tissues other than the placenta." In support of the rejection, the Examiner cites Daniel *et al.* (Am. J. Reprod. Immunol., 2000, 43:92-97) as disclosing that soluble VCAM-1 in serum is not predictive or diagnostic of the risk of spontaneous abortion.

Applicants respectfully traverse this rejection. Applicants submit that one of ordinary skill in the art could practice the claimed methods of the invention without undue experimentation.

In order for a claimed invention to be enabled, the standard is not whether or not experimentation is necessary to practice the claimed invention. Rather, the standard is whether or not the experimentation necessary to practice the claimed invention is undue (See *In re Wands*, 858 F.2d at 737). Thus, enablement is not precluded by the necessity for some experimentation, and a considerable amount of experimentation is permitted. *In re Wands*, supra. For [enablement of] a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner ***without undue experimentation*** [emphasis added]. MPEP 2164.02.

In the instant application, considerable direction and guidance is provided by the specification for how to measure gene expression in various biological samples (see, *e.g.*, pages 39-41) and how to determine whether such levels correlate with risk of spontaneous abortion. For example, as the Examiner acknowledges, the specification provides a detailed experiment (see, *e.g.*, Example 11 at page 54 and Figure 6) demonstrating that mRNA for various molecules in placental samples from abortion prone mice are present at elevated levels as compared to that from normal, control mice. The specification further provides that various embodiments of the invention include "determining the expression levels of one or more of the... genes in a tissue, cell, or biological fluid sample from a subject" and continues that

> ...in a preferred embodiment, the level of one or more of said genes in ***maternal serum or blood*** is determined. In a further preferred embodiment, the level of one or more said genes is determined in a ***placental sample***. The level of one or more of said genes may also be determined from an ***amniotic fluid sample*** or from a ***tissue sample*** such as a ***chorionic villous sample***. [emphasis added]

The Examiner cites Daniel *et al.* as disclosing that soluble VCAM-1 in serum does not correlate with pregnancy viability. Applicants submit, however, that the level of skill in the art at the time the instant application was originally filed was high. Thus further experimentation to determine whether a correlation exists between the expression levels of an adhesion molecule, immune cell

surface molecule or inflammatory cytokine at the mRNA level in a particular biological sample and risk of spontaneous abortion would not be undue. Therefore, Applicants are of the opinion that one or ordinary skill in the art could use the diagnostic and prognostic methods of the invention as applied to "biological samples" based upon the disclosures provided in the instant specification, coupled with information known in the art, without undue experimentation.

E. The Examiner contends that claim 5 is not enabled with respect to the recitation of "diagnostic method for determining whether a subject is suffering from spontaneous abortion." In particular, the Examiner states that there is insufficient enabling disclosure of the claimed method, *e.g.*, as to "what point in time relative to the loss of the products of conception the sample should be obtained to be of diagnostic value."

Based on the foregoing amendment of claim 5 to recite "diagnostic method for determining whether a subject is ***undergoing*** spontaneous abortion," this rejection should now be moot.

Rejection of Claims 1, 3, 5, 7 and 13-15 Under 35 U.S.C. 102(b)

Claims 1, 3, 5, 7 and 13-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Chaouat *et al.* (*J. Immunol.*, 1995, 154: 4261-4268). The Examiner relies on Chaouat *et al.* for teaching that "placentae of fetal resorption-prone mice, *i.e.*, those at increased risk and high incidence of spontaneous abortion, produce increased levels of inflammatory cytokines TNFα and IFN-γ, and reduced levels of anti-inflammatory cytokines IL-4 and IL-10, compared to a reproductively normal strain of mice..." The Examiner further states that Chaouat *et al.* review that "the levels of both mRNA and protein of inflammatory cytokines are locally elevated when compared to reproductively normal pregnancies." Finally, the Examiner relies upon Chaouat *et al.* for teaching that there is a "tight linkage between fetal rescue and the induction of an anti-inflammatory environment in the placenta." The Examiner concludes that the prognostic or diagnostic value of the levels of inflammatory cytokines in the placenta is inherent in the teachings of Chaouat *et al.* Applicants respectfully traverse the Examiner's assertion that the claimed invention is anticipated by Chaouat *et al.*

As amended, claims 1 and 5, and claims depending therefrom, are directed to a prognostic method for determining whether a subject is at risk for developing, or is undergoing, respectively, a spontaneous abortion, by detecting mRNA levels of specific molecules. Chaouat *et al.* fail to teach or suggest each and every element of the claimed invention. Specifically, Chaouat *et al.* fail to teach or suggest that altered mRNA levels of any one of the specifically claimed molecules can be used as a diagnostic or prognostic tool for spontaneous abortion. Indeed, Chaouat *et al.* fail to teach or suggest that the mRNA level of any cytokine can be used to diagnose/prognose spontaneous abortion. Accordingly, claims 1 and 5 are novel in view of the cited reference.

Rejection of Claims 1, 3, 5, 7 and 13-15 Under 35 U.S.C. § 103(a).

Claims 1, 3, 5, 7 and 13-15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Chaouat *et al.* (*J. Immunol.*, 1995, 154: 4261-4268) in view of Busfield (U.S. Patent No. 6,194,151). The Examiner relies on Chaouat *et al.* for the reasons set forth above. The Examiner admits that "Chaouat *et al.* do not exemplify determination of the mRNA levels of the corresponding cytokines." The Examiner further relies on Busfield for teaching that "nucleic acids and antibodies can be used in diagnostic and prognostic assays to detect protein and mRNA in biological samples, *e.g.*, in inflammatory diseases (see entire document, in particular, Uses and Methods of the Invention, columns 38-39)." The Examiner then concludes that:

> it would have been obvious to one of ordinary skill in the art at the time the invention was made to determine the risk of spontaneous abortion by detecting the levels of inflammatory cytokines in placental samples, as taught by Chaouat et al., by measuring the levels of the corresponding mRNA, as taught by Busfield. One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because, as reviewed by Chaouat et al., enhanced fetal death appears to correlate with, or even be mediated by, local NK activity and infiltration, perhaps through the stimulation of secretion of inflammatory cytokines (see page 2266, left column bottom paragraph). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success, because, as taught by Busfield, both protein and mRNA levels can be used in diagnostic and prognostic assays.

Applicants respectfully traverse this rejection. As described above, claims 1 and 5 are drawn diagnostic and prognostic methods method for determining whether a subject is at risk for

developing or is undergoing a spontaneous abortion by detecting the presence or level of mRNA of one or more specific molecules. The primary reference, Chaouat *et al.*, fail to teach or suggest that altered mRNA levels of any one of the specifically claimed molecules can be used as a diagnostic or prognostic tool for spontaneous abortion. Indeed, Chaouat *et al.* fail to teach or suggest that the mRNA level of any cytokine can be used to diagnose/prognose spontaneous abortion.

Moreover, the secondary reference, Busfield, fails to make up for the aforementioned deficiencies of Chaouat *et al.* Busfield fails to teach or suggest anything regarding spontaneous abortion, let alone the claimed diagnostic and prognostic methods which involve the detection of mRNA levels of specific molecules. Moreover, while Busfield teaches that both protein and mRNA levels ***can in principle*** be used in diagnostic and prognostic assays, Applicants argue that ***mRNA*** levels for a particular gene do not always directly correlate with, nor can they be expected to accurately predict, the ***protein*** levels for that gene, due in part to the dramatically different half lives of RNA and protein in a cell. Thus, prior to Applicants' direct demonstration that ***mRNA levels*** for various adhesion molecules, immune cell surface molecules and inflammatory cytokines are altered in the placentae of abortion-prone mice relative to that of normal mice, the predictive correlation for mRNA levels could not be assumed based upon any correlation demonstrated at the protein level.

Based at least on the foregoing, the pending claims are patentable in view of the cited references since the cited references fail to teach or suggest all of the claim limitations. Further, one of ordinary skill in the art would have had no motivation or likelihood of success in combining the cited references to arrive at the claimed methods.

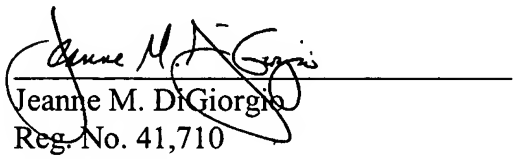
SUMMARY

In view of the foregoing amendments and arguments, reconsideration and withdrawal of all the rejections, and allowance of this application with all pending claims are respectfully requested. If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call (617) 227-7400.

Applicants believe no additional fee is due with this response. However, if an additional fee is due, please charge our Deposit Account No. 12-0080, under Order No. GNN-010CPDV from which the undersigned is authorized to draw.

Respectfully submitted,

LAHIVE & COCKFIELD, LLP



Jeanne M. DiGiorgio
Reg. No. 41,710
Attorney for Applicants

28 State Street
Boston, MA 02109
Tel. (617) 227-7400

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